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(54) Title: TERPYRIDINE-PLATINUM(II) COMPLEXES

(57) Abstract

A new class of 2,2':6',2"-terpyridine-platinum (II) and substituted 2,2':6',2"-terpyridine-platinum (II) complexes in which an N- or O- or halo nucleophile is the fourth ligand to platinum. The compounds are potent intercalators of DNA. Some have antitumour activity. Some have anti-parasitic activity. A new method of preparing the complexes involves reacting a Pt complex of 1,5-cyclooctadiene with a 2,2':6',2"-terpyridine.

TERPYRIDINE-PLATINUM(II) COMPLEXES

Background and Summary

This invention relates to a new class of 2,2':6',2"-terpyridine-platinum (II) and substituted 2,2':6',2"-terpyridine-platinum (II) complexes in which a N-, halo- or O-nucleophile is the fourth ligand to platinum. Such compounds are potent intercalators of DNA. Unexpectedly, those compounds with a fourth N-ligand and which carry a double positive charge also platinate selectively guanosine residues at N-7 in double stranded DNA. They react with all four free nucleosides found in DNA, but at very different rates. There is no precedent for nucleobases displacing a N-ligand from Pt(II). A new and highly efficient method has been developed for the synthesis of unsubstituted and substituted 2,2':6',2"-terpyridine-platinum(II) complexes.

The most effective compounds have antitumour activity comparable to or better than cisplatin and show little or no cross resistance. Such compounds are more effective than cisplatin against cisplatin-resistant cell lines. Other compounds of this class are most effective against doxorubicin resistant cell lines

Furthermore, this novel class of 2,2':6',2"-terpyridine-platinum (II) complexes possess anti-protozoal activity, against *Leishmania donovani, Trypanosoma cruzi, Trypanosoma brucei, and Plasmodium falciparum*.

2,2':6',2"-Terpyridine-platinum(II) complexes were first reported to bind to double stranded DNA by intercalation over twenty years ago, the duplex unwinding angle being comparable to that found with ethidium bromide [1]. An investigation of the binding of hydroxyethanethiol-2,2':6',2"-terpyridine-platinum(II) (1, R=SCH_2CH_2OH) with calf-thymus (ct)-DNA by fiber X-ray diffraction techniques showed the

or a halide ion,

R, R' and R" are the same or different and each is H, alkyl, aryl, aralkyl, alkaryl, acyl, halogen, haloalkyl, haloaryl, hydroxyalkyl, hydroxyaryl, aminoalkyl, aminoaryl, primary, secondary or tertiary amine, hydrazine, alkylhydrazine, alkoxy, aralkoxy, nitrile, ester, amide, nitro, azide or aziridino, or is a covalently linked chain which is joined to at least one other complex of the above structure so as to form a dimeric or oligomeric species,

R^3 is a positively charged group or is defined as R, R' and R",

each of R^4, R^5 and R^6 is alkyl, aryl, aralkyl or alkaryl or is a covalently linked chain which is joined to at least one other complex of the above structure so as to form a dimeric or oligomeric species,

and n is 1, 2 or 3,

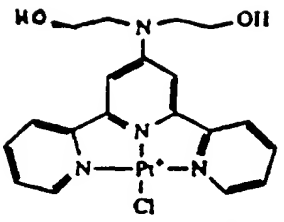
provided that when each of R, R' and R" is H, then X is not Cl.

Substituents may preferably be at the 4'-position of the terpyridine system and/or at the 3 or preferably 4 position of a pyridine ring at X. These substituents may be covalently linked by rigid or flexible chains of indeterminate length by which two or more of the structures may be joined to form dimers or oligomers. Dimeric and oligomeric species may preferably be formed through one or more of R^3, R^4, R^5 and R^6, e.g. R^3-R^3, R^4-R^4, R^5-R^5, R^6-R^6, R^3-R^4, R^3-R^5, R^3-R^6, R^4-R^5, R^4-R^6 or R^5-R^6.

R^3 may be a positively charged group such as an N-alkylated pyridine, an N-alkylated aromatic heterocycle or a quaternary ammonium salt.

Reference is directed to the accompanying drawings, in which Figure 1 is a graph of relative total carcinoma volume against time.

Examples of complexes in accordance with the invention are shown below.



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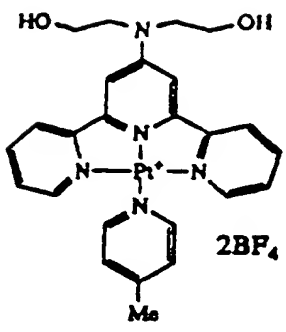

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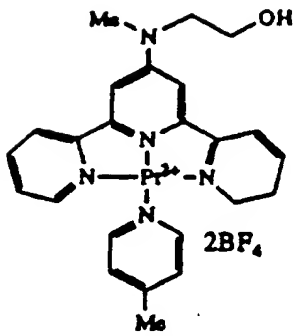

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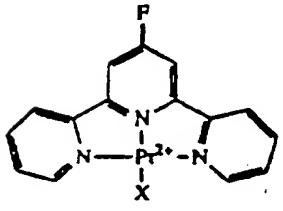

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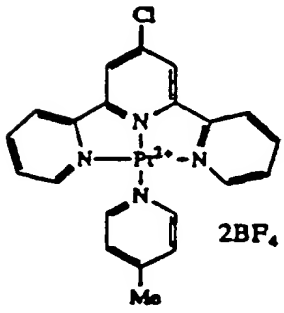

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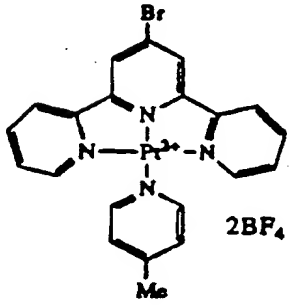

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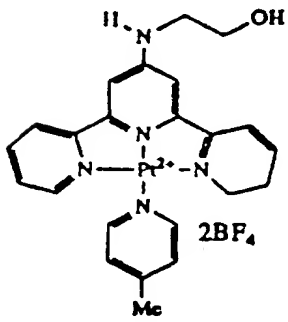

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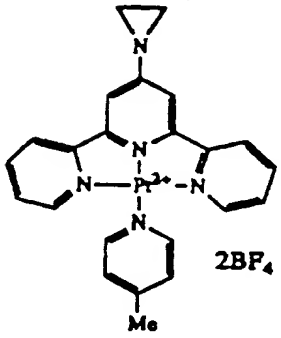

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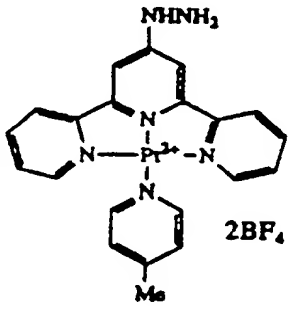

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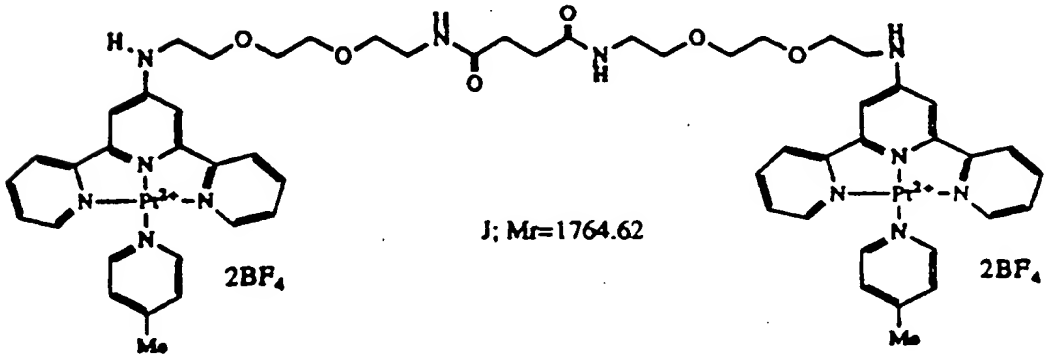


J; Mr=1764.62

DNA Binding Properties

In the expectation that a 2,2':6',2"-terpyridine-platinum(II) complex which retains a double positive charge would bind more effectively to DNA, 4-picoline-2,2':6',2"-terpyridine-platinum(II) (**A**), was prepared and its interaction with DNA investigated.

4-Picoline-2,2':6',2"-terpyridine-platinum(II) (**A**) was shown in a ligation assay to unwind and so intercalate into DNA. Circular dichroism was used to determine an equilibrium binding constant of approximately $2x10^7$ M^{-1} for the most stable binding mode of 4-picoline-2,2':6',2"-terpyridine-platinum(II) to poly[d(A-T)$_2$] with a site size of about 4 base pairs, and about $1x10^6$ M^{-1} for a second binding mode with a site size of about 2 base pairs. Fluorescence spectroscopy provided further evidence for the strong equilibrium binding constant of 4-picoline-2,2':6',2"-telpyridine-platinum(II) in that it displaces ethidium bromide bound to DNA. The double positive charge on 4-picoline-2,2':6',2"-terpyridine-platinum(II), together with the intercalative binding mode is probably responsible for the large binding constant.

Attempts to obtain crystals suitable for X-ray analysis of the complex of 4-picoline 2,2':6',2"-terpyridine-platinum(II) (**A**) with the self-complementary oligonucleotide d(CpGpTpApCpG) were unsuccessful. This oligonucleotide was chosen because of the availability of the high resolution structure of its complex with daunomycin, an intercalator of DNA with antitumour activity [5]. Good crystals were obtained, however, from a solution of 4,4'-vinylenedipyridine bis[2,2':6',2"-terpyridine platinum (II)] (**A**$_{14}$) and the oligonucleotide d(CpGpTpApCpG) but the crystals did not diffract X-rays to high resolution. From a series of NMR experiments it became clear that some nucleosides, especially guanosine, were able to slowly displace 4-picoline from 4-picoline 2,2':6',2"-terpyridine-platinum(II) (**A**) and the 4,4'-vinylenedipyridine linker from 4,4'-vinylenedipyridine bis[2,2':6',2"-terpyridine platinum (II)] (**A**$_{14}$). Although it is well established

Antitumour Activity

In the light of the above observations a number of unsubstituted and substituted 2,2':6',2"-terpyridine Pt(II) complexes were prepared and their antitumour activity investigated. The compounds were evaluated for *in vitro* cytotoxicity against five human ovarian carcinoma cell lines which included two selected for resistance to cisplatin (CHIcis^R and A2780cis^R) and one for resistance to doxorubicin (CHIdox^R). The compounds were exposed to cells for 96 h and growth inhibition assessed using the sulforhodamine B protein staining assay. The IC_{50} values (in μM) are shown in Table 1 and Table 2. Cisplatin was included for comparison.

The effect of the fourth ligand to platinum is seen from the data in Table 1.

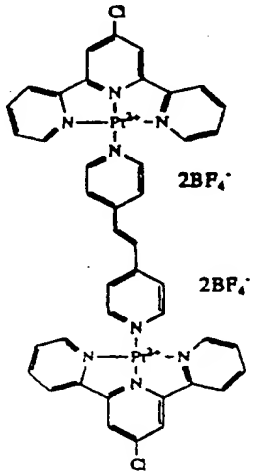
Compound (**A**) showed surprisingly variable antitumour activity (the mean value being presented). The potency of this compound may be particularly influenced by the status of the cells and the storage and dilution conditions used. The related dimer ($\mathbf{A}_{14}$) is very effective against CHI and A2780 cell lines and is significantly better than cisplatin against the corresponding cisplatin-resistant cells (CHIcis^R and A2780cis^R) indicating a lack of or low level of cross resistance. The effectiveness of compound ($\mathbf{A}_{14}$) may be due to the electrostatic repulsion between the two Pt(II) leading to facile nucleophilic displacement at Pt(II).

The effects of substituents at the 4'-position of the 2,2':6',2"-terpyridine tridentate ligand are shown in Table 2. It would appear that large and electron donating substituents as in compounds (**D**) and (**E**) lead to a significant loss of activity in general although with SKOV3 compound (**E**) is remarkably effective. All bisintercalators with flexible linkers generated through the 4'-position e.g. compounds (**J**), (**V**) and (**W**), have proved to be ineffective However, introducing the 4'-chloro group into the 2,2':6',2"-terpyridine tridendate ligand as in compound (**I**) provides an effective increase in activity against all cell lines, notably the CHI

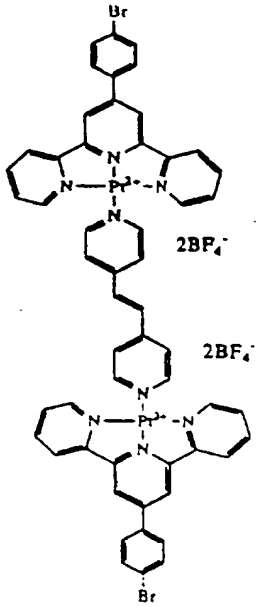
emesis [8], there is need for improvement in platinum-type antitumour agents. Cisplatin cross-links two nucleobases in DNA (most frequently guanosine)[6], whereas the 2,2':6',2"-terpyridine Pt(II) complexes intercalate into DNA and covalently platinate it, clearly providing a different mechanism of action which is reflected in the observation that it is effective against cisplatin-resistant cell lines.

Compound (**A**) was also administered as a single intraperitoneal injection in water to mice bearing subcutaneously implanted tumours e.g. ADJ/PC6 (according to the standard protocol for evaluating platinum complexes). The compound was toxic at a dose of 100mg/kg but there was no toxic affect at 50mg/kg giving a LD_{50} value of approximately 70mg/kg which is significantly better than cisplatin (LD_{50} approximately 10mg/kg).

In view of the effectiveness of compound ($\mathbf{A}_{14}$, Table 1) and of compound (**I** and **Q**, Table 2), a further generation of compounds has been prepared in which the most effective fourth ligand to Pt(II) and the most effective 4'-substituted in the 2,2':6',2"-terpyridine were incorporated into single molecules. Thus compounds ($\mathbf{I}_{14}$) and ($\mathbf{Q}_{14}$) have been made and tested. The data on these compounds is shown in Table 3.



(I_{14})



(Q_{14})

Elueze, S L Croft and D C Warhurst, J Antimicrobial Chemotherapy, 1996, 37, 511-518. The *in vitro* antimalarial activity of compounds were likewise determined according to their protocol. Mefloquin was used as the positive control."

SCREEN 2 - PROTOCOL II

The assays follow those outlined in Screen 1- Protocol 1 but include a range of doses in a dilution series from 30μM. Dose response curves were analysed by linear regression and ED_{50} values determined. *T. brucei* numbers/ml are determined using a Coulter Counter.

The data in Table 4 show the % inhibition caused by each of the 2,2':6',2"-terpyridine Pt(II) complexes where the fourth ligand X to Pt(II) is changed. For *Leishmania donovani* and *Trypanosoma cruzi* the most effective compounds are ($\mathbf{A_{11}}$) and ($\mathbf{A_{12}}$) i.e. where the fourth ligand is water or ammonia. For *Trypanosoma brucei* the most effective compounds are (**A**) and ($\mathbf{A_1}$), i.e. where the fourth ligand is 4-methyl-pyridine and 4-bromo-pyridine.

The data in Table 5 show the effect of changing the substituent at the 4'-position on the 2,2':6',2"-terpyridine Pt(II) complex keeping the fourth ligand X as 4-picoline. For *Leishmania donovani* compounds (**P**) and (**Q**) are remarkably effective at 1 μM. For *Trypanosoma cruzi* compound (**I**), (**R**) and (**S**) were about as effective at 1 μm but for synthetic expediency and because compound (**I**) was the most effective compound for *T. brucei* this was selected for further development. In the light of these results, the following third generation of compounds were prepared and their antiprotozoal activity investigated. The data is shown in Table 6.

Directed Enzyme Prodrug Therapy (ADEPT) and Gene Directed Enzyme Prodrug Therapy (GDEPT). Alternatively the effectiveness of antitumour agents can be significantly enhanced by covalently linking them to polymers which are selectively taken up by tumour cells by the EPR (enhanced permeability and retention) effect. If the polymer drug conjugate linkage is susceptible to proteolysis by endosomal or lysosomal proteases then the drug is released intracellularly within the tumour cell leading to an improved therapeutic index.

The 4'-azido-2,2':6',2"-terpyrine Pt(II) complex (**Z**) and bis-intercalators from this Pt(II) complex e.g. ($\mathbf{Z}_{14}$) where the linker is 4,4'-vinylidenedipyridine, have been developed as tools for molecular biology. A family of bis-intercalators based on the 4'-azido-2,2':6',2"-terpyrine Pt(II) moiety are of general interest since they are able to crosslink two duplexes of DNA which are in close proximity and by photoactivating the azido group covalently cross-link the two DNA duplexes. Since DNA duplexes come close together at sites of replication, genetic recombination and topoisomerase action these molecules will be useful tools to investigate these processes as well as for studying the topology of packaged DNA, e.g. in chromosomes.

New Synthetic Procedure for the Synthesis of Unsubstituted and Substituted 2,2':6',2" -Terpyridine-platinum(II) Complexes

The standard procedure for the preparation of 2,2':6',2"-terpyridine-platinum(II) complexes was used initially for the preparation of compound (**A**), but this method is not satisfactory for many of the Pt(II) complexes. A new and highly efficient preparative procedure has been developed.

Most (2,2':6',2"-terpyridine)platinum(II) complexes have been prepared from chloro(2,2':6',2"-terpyridine)platinum(II) chloride ($\mathbf{A}_{13}$), which can be synthesised by heating K_2PtCl_4 and 2,2':6',2"-terpyridine in aqueous

The method (**Scheme 1**) involves treatment of $Pt(COD)Cl_2$ or $Pt(COD)I_2$ with silver tetrafluoroborate in acetone at room temperature for a few minutes followed by centrifugation to remove the silver halide precipitate. To the clear solution is added a solution of 2,2':6',2"-terpyridine in acetonitrile at room temperature. A pale yellow complex precipitates from the solution after stirring at room temperature for 15-30 min. This acetonitrile complex is washed with acetone to remove any unreacted starting materials then treated with excess of the fourth ligand, e.g. 4-picoline in acetonitrile for a few minutes at room temperature to give 4-picoline 2,2':6':2"-terpyridine platinum (II) tetrafluoroborate (**A**) which precipitates from solution on addition of diethyl ether. Recrystallisation of the complex from acetonitrile by slow diffusion of diethyl ether vapour gave the pure complex in very good yield. Its ^1H nmr and mass spectra were identical to the material obtained from the reaction of $[Pt(terpy)Cl]^+$ and 4-picoline in the presence of silver tetrafluoroborate reported in the experimental section. The method has been applied to many other 4'-substituted-2,2':6'2"-terpyridines starting with $Pt(COD)I_2$, to give the desired products which, in all cases, were isolated as the tetrafluoroborate salts in 70-85% yield after recrystallisation. All the complexes gave correct mass and isotope pattern (ES-MS), ^1H nmr spectra and satisfactory elemental analyses.

The presence of the COD ligand in the starting material is necessary for labilising the halide ligands and thus initiating the reaction. Similar reactions starting from $Pt(MeCN)_2Cl_2$ and $Pt(DMSO)_2Cl_2$ required heating for several hours and gave the less reactive chloro(2,2':6',2"-terpyridine)platinum(II) complex. The choice of solvent has a significant effect on the success of this method. Methanol may be used in place of acetone but acetonitrile alone gave unsatisfactory results because the silver halides were not precipitated completely even in the presence of excess silver ion. The presence of acetonitrile enables the intermediate

afforded 4-picoline-2,2 ':6':2 "-terpyridine-platinum(II) tetrafluoroborate (35.1 mg) as bright yellow needles (m.p. > 220°C); υ_{max} (KBr disc) 3387br s, 3083br m, 3032br m, 1606s, 1477m, 1453s, 1400m, 1318m, 1056br vs, 776vs and 722m cm^{-1}; λ_{max} (ε) (H_2O) 240 (28800), 269 (19000), 324 (8700) and 339 (15000) nm; $^{\delta}H$ (5OOMHz, D_2O) 2.59 (3H, s, -C$\underline{H}_3$), 7.65 (2H, m, 2 x C(5)$\underline{H}$), 7.70 (2H, d, $\underline{J}$ = 6.3 Hz, 2 x C(8)$\underline{H}$), 7.77 (2H, d, $\underline{J}$ = 5.6 Hz, 2 x C(6)$\underline{H}$), 8.34-8.37 (4H, m, 2 x C(4)$\underline{H}$ and 2 x C(3)$\underline{H}$, 8.36 (2H, d, $\underline{J}$ = 9.0 Hz, 2 x C(3')$\underline{H}$), 8.47 (1H, t, $\underline{J}$ = 8.3 Hz, C(4')$\underline{H}$), 8.79 (2H, d, $\underline{J}$ = 6.6 Hz, 2 x C(7)$\underline{H}$); m/z (ESI) 260.5 ([4-picoline-terpyridine-Pt(II)]$^+$, 100%).

4-Picoline-2,2':6':2"-terpyridine-platinum(II) tetrafluoroborate (**A**) was also prepared in 77% yield (isolated crystalline product) by the new method of synthesis starting with Pt(COD)I_2. It was identical with the product described above.

To a suspension of diiodo(1,5-cyclooctadiene)platinum (II) (55mg, 0.10 mmol) in acetone[1,2] (1 ml) in an Eppendorf tube was added silver tetrafluoroborate (40 mg, 0.21 mmol). The resulting mixture was stirred at room temperature until a clear colourless solution with a pale yellow precipitate of AgI obtained (typically 2-3 min) then the precipitate was centrifuged off and discarded. The solution was added to a suspension of 2,2':6',2"-terpyridine (18.7 mg, 0.08 mmol) in acetonitrile (0.5 ml) and the reaction mixture stirred at room temperature for another 30 min. The yellow crystals of the acetonitrile complex formed were collected by centrifugation and washed with acetonitrile and the crystals re-suspended in acetonitrile. 4-Picoline (10 µl, excess) was then added and the reaction mixture stirred at room temperature for a few minutes to give a clear solution. The picoline complex was precipitated by addition of diethyl ether and washed with ether. Recrystallisation from acetonitrile or methanol gave compound (**A**) as yellow needles (43 mg, 77%) m.p. >200°C (dec) (Found C, 36.5, H, 2.0, N, 8.2 % $PtC_{21}H_{18}N_4B_2F_8$ requires C, 36.3, H, 2.6, N, 8.1%). δ_H (200 MHz, CD_3CN) 2.64 (3H, s,

complex (contaminated by trace of guanosine) in quantitative yield. δ_H (500 MHz, $2H_2O$) 3.82 (1H, dd, *J*= 12.8, 4.1 Hz, CHaHbOH), 3.91 (1H, dd, *J*= 12.7, 2.9 Hz, CHaHbOH), 4.28 (1H, m, H4'), 4.43 (1H, t, *J*=4.8 Hz, H3'), 4.82 (1H, t, *J*=5.0 Hz, H2'), 6.10 (1H, d *J*=4.8 Hz, H1'), 7.65 (2H, m, terpy H5,5"), 7.92 (2H, dd *J*=11.5, 5.6 Hz,terpy H6,6"), 8.32-8.36 (6H, m, terpy H3,3", H4,4" and H3',5'), 8.49 (1H, t *J*=5.0 Hz, terpy H4'), 8.95 (1H, s, guanine-H8).; m/z (ES MS) 355.78 (M2+, 100%).

Isolation and characterisation of N1-[(2,2':6' 2"-terpyridine)platinum(II)]-N6-[(2,2':6',2"-terpyridine)platinum(II)]adenosine and N1-[(2,2':6',2"-terpyridine)platinum(II)]-N6-[(2,2':6',2 "-terpyridine)platinum(II)]l -2 '-deoxyadenosine

(a) from compound (**A**): compound(**A**) (13.9 mg, 20 μmol) and adenosine (26.8 mg, 100 μmol) were dissolved in 1.8 ml of deionised water (1.8 ml). Sodium phosphate buffer pH 5.5 (0.5 M, 200 μL) was added and the solution was incubated at 37°C for 10 days. The deep orange solution was first purified on a column of Sephadex G-15 followed by chromatography on a column of Sephadex G-10. The orange fractions were collected and freeze dried to give the product as a red powder (~5 mg) δ_H (500 MHz, $2H_2O$) 3.96 (2H, m, CH_2OH)), 4.39 (1H, m, H4'), 4.50 (1H, dd, *J*=5.6, 3.5 Hz, H3'), 4.90 (1H, dd, *J*=6.0, 5.5 Hz, H2'), 6.23 (1H, d *J*=6.2 Hz, H1'), 7.50 (4H, 2xt, terpyl-H5,5" and terpy2-H5,5"), 8.05 (2H, dd, *J*=10.1, 4.6 Hz, terpy 1-H6,6"), 8.10 (4H, 2xd, terpy 1-H3,3" and terpy2-H3,3"), 8.15 (4H, 2xd, terpy1-H3',5' and terpy2-H3',5'), 8.25 (4H, 2xt, terpy1-H4,4" and terpy2-H4,4"), 8.42 (2H, br m, terpy2-H6,6"), 8.48 (2H, 2xt, terpy1-H4' and terpy2-H4'), 8.55 (1H, s, adenine-H8), 8.85 (1H, s, adenine-H2).

(b) from compound (A_{13}): A solution of [Pt(terpy)Cl]Cl.$2H_2O$ (53.5 mg, 100 μmol) and silver nitrate (35.0 mg, 200 μmol) was heated at

Isolation and characterisation of N3-[(2,2':6',2"-terpyridine)platinum(II)]-N4-[(2 ,2 ':6',2 "-terpyridine)platinum(II)]-2'-deoxycytidine

(a) from compound (**A**): as for the guanosine and adenosine complex starting from [Pt(terpy)(4-picoline)](BF4)2 (**A**) (13.9 mg, 20 μmol) and 2'-deoxycytidine (22.6 mg, 100 μmol). The product which precipitated from the solution upon addition of a saturated aqueous solution of sodium tetrafluoroborate, was collected by centrifugation and recrystallised from water (5 mg, 37 %), mp>200°C; (Found: C, 34.0; H, 2.1; N, 8.8. $C_{39}H_{34}N_9O_4Pt_2B_3F_{12}.0.3NaBF_4$ requires C, 34.0, H, 2.5, N, 9.1 %); δH (200 MHz, ^2H_2O) 2.52 (2H, m, H2'), 3.88 (2H, m, C<u>H</u>$_2$OH), 4.12 (1H, m, H4'), 4.55 (1H, m, H3'), 6.42 (1H, t, *J*=6.7 Hz, H1'), 6.60 (1H, d *J*=7.8 Hz, cytosine-H5) 7.50-7.56 (4H, m, 2 x terpy-H5,5"), 7.82 (1H, d, *J*=7.8 Hz, cytosine-H6), 8.0-8.5 (18H, m, terpy-H); m/z (ES MS) 360.95 (M3+, 100%).

(b) from compound (A_{13}): A solution of [Pt(terpy)Cl]Cl $2H_2O$ (26.7 mg, 50 μmol) and silver nitrate (17 mg, 100 μmol) in deionised water (1.0 ml) was heated at 70-80°C in a water bath for 2 h. The AgCl precipitate was centrifuged off, the solution added to 2'-deoxycytidine (11.8 mg, 52 μmol), and the solution heated for another 2 h at 70-80 °C. After centrifugation, the product was precipitated by addition of sodium tetrafluoroborate and recrystallised from water to give the complex as red microneedles (25 mg, 70 %). Counterion exchange with ammonium hexafluorophosphate in water provided the red hexafluorophosphate in quantitative yield. δH (500 MHz, C^2H_3CN) 2.34 (m, 2H, 2 x H2'), 3.22 and 3.35 (2H, 2 x br s, 2 x OH), 3.78 (1H, dd, *J*= 12.0, 3.6 Hz, C<u>H</u>aHbOH), 3.84 (1H. dd, *J*= 12.0, 3.3 Hz, CHa<u>H</u>bOH), 3.96 (1H, dd, *J*= 11.2, 3.6 Hz, H4'), 4.43 (1H, m, H3'), 6.26 (1H, t *J*=6.3 Hz. H1'), 6.37 (1H. d *J*=7.8 Hz. cytosine-H5), 6.84 (1H, br s. cytosine-N6<u>H</u>), 7.44-7.54 (4H, m. 2 x terpy-H5.5"), 7.88-8.00 (9H. m. 2 x terpy-H3.3", 2 x terpy-H3'.5' and cytosine-H6). 8.13-8.21 (6H. m. 2 x terpy-H4.4" and terpy1-H6.6"). 8.27 (2H. ddd. J=

C(6), C(6")); 137.49 (2C, C(4), C(4")); 123.49 (1C, C(5), C(5")); 121.94 (1C, C(3), C(3")); 103.91 (1C, C(3'), C(5')); 58.72 (1C, $H_2\underline{C}OH$; 52.86 (1C, $H_2\underline{C}$Nterpy). m/z (ESI) : 377 (MH^+). Anal. Calcd. for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 6.00; N, 16.65. Found C, 67.59; H, 6.02; N, 16.41.

Isolation and characterisation of the two alkoxy side products. The dichloromethane filtrate remaining from the recrystallisation was evaporated *in vacuo* and the solid residue chromatographed on an alumina preparative plate using P.E. / EtOAc 7 / 1 as eluant and carrying out two elutions to allow a better separation. Three bands were obtained and identified as 4'-chloro-2.2':6'.2"-terpyridine, 4'-methoxy-2,2':6',2"-terpyridine and 4'-ethoxy-2,2':6',2"-terpyridine .

4'-Methoxy-2,2':6',2"-terpyridine. mp 56-57°C. TLC (alumina, P.E. / EtOAc 3 / 1) : R_f = 0.53. δ_{1H} (200 MHz, $CDCl_3$) : 8.71 (*d*, ^3J(6,5) = 4.7, 2H, H-C(6), H-C(6")); 8.64 (*d*, ^3J(3,4)=8.0, 2H, H-C(3) , H-C(3")); 8.04 (*s*, 2H, H-C(3'), H-C(5')); 7.87 (*dt*, ^4J(4,6) = 1.8, ^3J(4,3) = ^3J(4,5) = 7.8, 2H, H-C(4), H-C(4")); 7.34 (*ddd*, ^4J(5,3) = 1.1, ^3J(5,6) = 4.8, ^3J(5,4) = 7.5, 2H, H-C(5), H-C(5")); 4.05 (*s*, 3H, $\underline{H}_3$-COterpy). δ_{13C} (50.3 MHz, $CDCl_3$) : 168.15 (1C, C(4')); 157.35 (2C, C(2) or C(2'), C(6') or C(2")); 156.33 (2C, C(2) or C(2'), C(6') or C(2")); 149.28 (2C, C(, C(6), C(6")); 137.04 (2C, C(4), C(4")); 124.03 (1C, C(5), C(5")); 121.54 (1C, C(3), C(3")); 107.05 (1C, C(3'), C(5')); 55.55 (1C, $H_3\underline{C}$Oterpy). m/z (ESI) : 264 (MH^+). This compound can be prepared in excellent yield by methanolysis of 4'-chloro-2.2':6'.2"-terpyridine activated by $FeCl_2.4H_2O$.

4'-Ethoxy-2,2':6',2"-terpyridine. mp 85-86°C. TLC (alumina, P.E. / EtOAc 3 / 1) : R_f = 0.59. δ_{1H} (200 MHz, $CDCl_3$) : 8.70 (*d*, ^3J(6,5) = 4.1, 2H, H-C(6), H-C(6")); 8.63 (*d*, ^3J(3,4)=8.1, 2H, H-C(3) , H-C(3")); 8.02 (*s*, 2H, H-C(3'), H-C(5')); 7.86 (*dt*, ^4J(4,6) = 1.8, ^3J(4,3) = ^3J(4,5) = 7.3, 2H, H-C(4), H-

8.65 (d, ^3J(6,5)=4.5, 2H, H-C(6), H-C(6")); 8.60 (d, ^3J(3,4)=8.5, 2H, H-C(3), H-C(3")); 7.83 (dt, ^3J(4,5)=7.77, ^4J(4,6)=1.8, 2H, H-C(4), H-C(4")); 7.78 (s, 2H, H-C(3'), H-C(5')); 7.30 (ddd, ^3J(5,4)=7.4, ^3J(5,6)=4.8, ^4J(5,3)=1.1, 2H, H-C(5), H-C(5")); 3.9 (t, $^3J_{vic}$=5.8, 2H, terpyNMe.$CH_2C\underline{H}_2OH$); 3.7 (t, $^3J_{vic}$=5.8, 2H, terpyNMe. $C\underline{H}_2CH_2OH$); 3.2 (s, 3H, terpyN$C\underline{H}_3$.CH_2CH_2OH).

4'-(1-Methylhyrazino)-2,2':6',2"-Terpyridine

4'-Chloro-2,2':6',2"-terpyridine (148mg, 0.55mmol) was dissolved in isobutanol (3ml) with warming. Excess methylhydrazine (0.8ml) was added. The mixture was then heated to reflux, with stirring, for 28 hrs. On cooling white needles crystallised out of solution. The solid was collected by filtration and washed with a few drops of diethyl ether to yield analytically pure 4'-(1-methylhyrazino)-2,2':6',2"-terpyridine (132mg, 86%): m.p 217-219°C; (Found: C, 69.6; H, 5.05; N, 25.2. $C_{16}H_{15}N_5$ requires C, 69.3; H, 5.4; N, 25.2); ν_{max}(KBr)/cm^{-1} 3323(m), 3100-2700(w,br), 2359(w,br), 1562(s), 1582(s), 1470(s), 1408(s), 1093(m), 1005(m), 826(w); δ_{1H} (200 MHz; $CDCl_3$) 8.70 (d, ^3J(6,5)=4.7, 2H, H-C(6), H-C(6")); 8.64 (d, ^3J(3,4)=7.98, 2H, H-C(3), H-C(3")); 7.98 (s, 2H, H-C(3'), H-C(5')); 7.85 (dt, ^3J(4,5)=7.56, ^4J(4,6)=1.77, 2H, H-C(4), H-C(4")); 7.33 (ddd, ^3J(5,4)=7.4, ^3J(5,6)=4.8, ^4J(5,3)=1.2, 2H, H-C(5), H-C(5")); 4.06 (s, 2H. terpyNMe.$N\underline{H}_2$); 3.40 (s, 3H, terpyN$C\underline{H}_3$.NH_2); m/z (ESI)= 278 (100% , $[MH]^+$).

4'-Hydrazino-2,2':6',2"-Terpyridine

4'-Chloro-2,2':6',2"-terpyridine (600mg, 2.2mmol) was dissolved in isobutanol (12ml) with warming. Excess hydrazine (4ml) was added. The mixture was then heated to reflux under argon, with stirring, for 30 hours. On cooling white crystals precipitated out of solution. These were collected by filtration and washed with a few drops of water to yield

4'-(*N*-2-Chloroethyl)amino-2,2':6',2"-Terpyridine

A solution of 4'-(*N*-2-hydroxyethyl)amino-2,2':6',2"-terpyridine (880mg, 3mmol) in thionyl chloride (8ml) was kept at room temperature for 20 hours. Excess thionyl chloride was removed *in vacuo* to leave a green glassy solid. This solid was suspended in dichloromethane (40ml) and dissolved, with effervescence, when washed with saturated aq. sodium bicarbonate solution (2x25ml). The aq. phase was separated and re-extracted with further DCM. The organic extracts were then combined and dried over anhydrous magnesium sulphate. Filtration and evaporation of the solvent *in vacuo* gave a solid which was purified by elution through a column of activity IV neutral alumina. Initially 100% DCM then 50:1 DCM:methanol were used as eluant. Impurities remained on the base line. Removal of solvent *in vacuo* from the collected fractions yielded the 4'-(*N*-2-chloroethyl)amino-2,2':6',2"-terpyridine (797mg, 85%). Recrystallisation was achieved from diethyl ether/P.E. (40-60°C): m.p.135-137°C; (Found: C, 66.0; H, 4.5; N, 18.3. $C_{17}H_{15}N_4Cl$ requires C, 65.7; H, 4.8; N, 18.0); ν_{max}(KBr)/cm^{-1} 3256(m,br), 3134-2954(w,br) 1582(s), 1565(s), 1460(m), 1443(m), 1226(m), 985(m), 793(s); δ_{1H} (500 MHz; $CDCl_3$) 8.68 (d, ^3J(6,5)=4.7, 2H, H-C(6), H-C(6")); 8.62 (d, ^3J(3,4)=7.97, 2H, H-C(3), H-C(3")); 7.84 (dt, ^3J(4,3)=^3J(4,5)=7.7, ^4J(4,6)=1.79, 2H, H-C(4), H-C(4")); 7.73 (s, 2H, H-C(3'), H-C(5')); 7.32 (ddd, ^3J(5,4)=7.4, ^3J(5,6)=4.8, ^4J(5,3)=1.1, 2H, H-C(5), H-C(5")); 4.79 (t, $^3J_{VIC}$=5.2, 1H, terpyN<u>H</u>.CH_2CH_2Cl); 3.83-3.74 (m, 4H, terpyNH.$C\underline{H}_2C\underline{H}_2Cl$); m/z(ESI)=†311.18 (100%, $[MH]^+$).

4'-Aziridino-2,2':6',2"-Terpyridine

Sodium hydride (16mg, 0.6mmol) was washed with P.E. (40-60°C) and suspended in tetrahydrofuran (1ml). *t*-Butanol (38ml, 0.4mmol) was added and the mixture stirred for 5 min. until effervescence had subsided. After this time a solution of 4'-(*N*-2-chloroethyl)amino-2,2':6',2"-

Synthesis of 4'(4-bromophenyl)-2,2':6,2"-terpyridine

A mixture of 4-bromobenzaldehyde (7.40 g, 40 mmol), 2-acetylpyridine (10.0 g, 82 mmol), acetamide (35 g) and ammonium acetate (25 g) was heated in an oil bath at 180°C for 2 hr. The reaction mixture was cooled to 120°C and aqueous sodium hydroxide (18 g in 50 ml H_2O) was carefully added. The reaction was maintained at 120°C for another 2 hr. The aqueous phase was decanted while still hot. The residue was washed with water then dissolved in a small volume of warm glacial acetic acid. Concentrated HBr (48%, 100 ml) was added and the resulting suspension was kept in the fridge for 2-3 hr. The glossy precipitate of HBr salt was filtered by a sintered glass funnel and washed with 48% HBr then sucked to dryness. The solid was transferred to a flask with 50 ml of water. Aqueous sodium hydroxide (~ 5 M) was added dropwise with stirring until the solution is just basic to litmus (pH=8). The white suspension was extracted with dichloromethane (3x100 ml). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to give the crude product as a light brown residue (about 4 g). ^1H nmr spectrum showed about 20% of contaminant which was removed as follows.

The residue from above (max. 4 g, 10 mmol) was heated to reflux with $FeCl_2.4H_2O$ in ethanol (50 ml) for 1 hr. The deep purple precipitate was centrifuged and washed several times with ether. The precipitate was dried and dissolved in aqueous acetonitrile 1:1. Aqueous sodium hydroxide (~5 M) was added dropwise until pH=10. The solution was then stirred vigorously under oxygen atmosphere until the purple colour was completely discharged (about 2 hr., more base may be added if necessary). The brown suspension was extracted with ether (5x100 ml). The ether layer was dried and evaporated *in vacuo*. The residue was recrystallised from ethanol to give the pure product as white fluffy needles (2.19 g): m.p. 139-141°C; δ_H (200 MHz. $CDCl_3$) 7.38 (dd J=6.1 J'=3.7 Hz, 2H. H4,4" or H5,5"), 7.66 and 7.81 (AB system J=8.6 Hz, 4H. H2,6 and

4'-Azido-2,2':6',2"-terpyridine

A solution of 4'-hydrazino-2,2':6',6"-terpyridine (0.263g ; 1.0mmol) in acetic acid (2.0ml) and water (1.0ml) was treated dropwise at 0°C with a cold solution of sodium nitrite (0.69g ; 10mmol) in water (2.0ml). A pale brown solid was precipitated. When the addition was complete, ether (20ml) was added and the aqueous layer made alkaline by the addition of solid sodium hydroxide beads. The solid dissolved and the aqueous phase was further extracted with ether (2 x 20ml). The combined organic extracts were dried and evaporated to give the title compound as a pale yellow brown solid (0.273g ; 99%). Crystallisation from methanol-dichloromethane gave pale yellow needles mp. 140-141°C (Found: C, 65.7; H, 3.6; N, 30.5. $C_{15}H_{10}N_3$ requires C, 65.7; H, 3.7; N, 30.6%); ν_{max}(nujol)/cm^{-1} 2109 (N3); δ_H(200MHz $CDCl_3$) 7.37 (2H, ddd, *J* 1.0, 4.8 and 5.9, terpy H5,5"),7.87 (2H, td, *J* 1.8, 7.8, terpy H4,4"), 8.16 (2H, s, terpyH3',5'), 8.63 (2H, d, *J* 8.0, terpyH3,3") and 8.68-8.74 (2H, m, terpyH6,6"); δ_C(50MHz $CDCl_3$) 111.1, 121.3, 124.1, 136.8, 149.1, 150.8, 155.2, 157.1; m/z(ESI) 275(MH^+).

4'-Amino-2,2':6',2"-terpyridine

A solution of 4'-azido-2,2':6',6"-terpyridine (0.453g ; 1.65mmol) in dichloromethane (5.0ml) and methanol (5.0ml) was saturated with hydrogen sulphide at 0°C and the solution kept at room temperature for 4h by which time tlc showed no azide to remain. The solution was degassed with argon to remove hydrogen sulphide and then evaporated to dryness. The residue was treated with sulphuric acid (2M, 3.0ml) and the aqueous mixture filtered and washed with dichloromethane to remove elemental sulphur. The solution was basified by the dropwise addition of sodium hydroxide (50%) and extracted with dichloromethane (3 x 20ml). The combined organic layers were dried and evaporated to give the title compound as a pale yellow solid.(0.398g ; 97%). Crystallisation from light

H, 2.7; N, 12.3. $PtC_{22}H_{22}N_6B_2F_8.CH_3CN$ requires C, 36.9; H, 3.2; N, 12.5); ν_{max}(KBr)/cm^{-1} 3359(m), 3093(m,br), 2251(w), 1646-1609(s,br), 1212(m), 1150-950(s,br), 785(s); δ_{1H} (500 MHz; CD_3CN)* 8.82 (dd with broad ^{1}H-^{195}Pt satellites, ^3J(2,3)=5.2, ^5J(2,5)=1.4, 2H, picoline H-C(2), H-C(6)); 8.35-8.15 (m, br, 4H, H-C(3), H-C(3"), H-C(4), H-C(4"); 7.73 (dd, ^3J(3,2)=5.6, ^5J(3,6)=1.00, 2H, picoline H-C(3), H-C(5)); 7.70 (d, ^3J(6,5)=6.6, 2H, H-C(6), H-C(6")); 7.62 (ddd, ^3J(5,4)=7.3, ^3J(5,6)=6.0, ^4J(5,3)=2.0, 2H, H-C(5), H-C(5")); 4.71 (s, 2H, terpyNMe.N$\underline{H}_2$); 3.55 (s, 3H, terpyNC$\underline{H}_3$NH$_2$); 2.63 (s, 3H, picoline C$\underline{H}_3$); m/z (ESI)= 282.8(95%, $[M]^{2+}$). *H-C(3'), H-C(5') resonance not observed at high temperature or by COSY.

(4-Picoline)(4'-(*N*-2-Hydroxyethyl)amino-2,2':6',2"-Terpyridine) Platinum (II) Tetrafluoroborate (U)

The general procedure for platination was carried out using acetone as the initial solvent and 4'-aziridinoterpyridine (24mg, 0.086mmol). Recrystallisation from acetonitrile gave the title compound as orange crystals (41mg, 63%): m.p >200°C; (Found: C, 35.7; H, 2.8; N, 9.2. $PtC_{23}H_{23}N_5OB_2F_8.H_2O$ requires C, 35.7; H, 3.2; N, 9.1); ν_{max}(KBr)/cm^{-1} 3349(m,br), 3103(m,br), 1626(s,br), 1482(s), 1360(m), 1213-1083(s,br), 786(s); δ_{1H} (200 MHz; CD_3CN) 8.81 (d, br with broad ^{1}H-^{195}Pt satellites, 2H, picoline H-C(2), H-C(6)); 8.38-8.20 (m, br, 4H, H-C(3), H-C(3"), H-C(4), H-C(4")); 7.80-7.68 (m, br, 4H, H-C(5), H-C(5"), picoline H-C(3), H-C(5)); 7.60 (s, br, 2H, H-C(6), H-C(6")); 7.40 (s, br, 2H, H-C(3'), H-C(5')); 6.90 (s, br, 1H, terpyN$\underline{H}$.CH$_2$CH$_2$OH); 3.78 (t, $^3J_{vic}$=5.0, 2H, terpyNH.CH$_2$C$\underline{H}_2$OH); 3.58 (q, $^3J_{vic}$=5.1, 2H, terpyNH.C$\underline{H}$2CH2OH); 3.30-3.20 (s, br, 1H, terpyNH.CH$_2$CH$_2$O$\underline{H}$); 2.62 (s, 3H, picoline C$\underline{H}_3$); m/z (ESI)= 290.33 (95%, $[M]^{2+}$).

the terpyridine moiety and therefore it is probably more AgI. Addition of diethyl ether to the supernatant yielded a tarry solid which became crystalline on trituration with further Et_2O. These crystals were collected by filtration and recrystallised from MeCN by diffusion of Et_2O to yield the title compound (56mg, 82%): m.p >200°C; (Found: C, 36.6; H, 3.2; N, 9.4. $PtC_{23}H_{21}N_5B_2F_8.H_2O$ requires C, 36.6; H, 3.1; N, 9.3); ν_{max}(KBr)/cm^{-1} 3500-3200(w,br), 3080(w,br), 1610(m), 1480(m), 1436(m), 1298(w), 1058(s,br), 792(m); δ_{1H} (500 MHz; CD_3CN) 8.81 (dd, br with broad ^{1}H-^{195}Pt satellites, ^3J(2,3)=5.3, ^5J(2,5)=1.3, 2H, picoline H-C(2), H-C(6)); 8.40 (dt, ^3J(4,3)=7.89, ^4J(4,6)=1.59, 2H, H-C(4), H-C(4")); 8.31 (d, br, ^3J(3,4)= 7.86, 2H, H-C(3), H-C(3")); 7.97 (s, 2H, H-C(3'), H-C(5')); 7.75 (dd, ^3J(3,2)=5.6, ^5J(3,6)=1.2, 2H, picoline H-C(3), H-C(5)); 7.71 (d, br, ^3J(6,5)= 6.29, 2H, H-C(6), H-C(6")); 7.68 (ddd, ^3J(5,6)=5.87, ^4J(5,3)=1.6, 2H, H-C(5), H-C(5")); 2.64 (s, 3H, picoline C$\underline{H}_3$); 2.61 (s, 4H, aziridine C$\underline{H}_2$'s); m/z (ESI)=281.3(100%, $[M]^{2+}$).

Adipoyl-Linked Bis[4'-Hydrazino-2,2':6',2"-Terpyridine]

Adipoyl chloride (175µl, 1.2mmol) was added to a solution of 4'-hyrazinoterpyridine (178mg, 2.2mmol) in 10ml of tetrahydrofuran. Immediately the solution turned yellow and a yellow solid became suspended in solution. After stirring at room temperature for 2 hours dichloromethane (100ml) and saturated aq. sodium bicarbonate solution (100ml) were added. The yellow solid turned white and collected at the solvent interface. Isolation of this solid by filtration, and washing with diethyl ether yielded the titled product (387mg, 55%). A sample for elemental analysis was prepared as the acetate salt: m.p >200°C; (Found C, 63.8; H, 5.2. $C_{36}H_{32}N_{10}O_2.C_4H_8O_4$ requires C, 63.5 H, 5.3). ν_{max}(KBr)/cm^{-1} 3283-3012(s,br). 2928-2800(w,br). 1655(s). 1585(s). 1566(s). 1467(s).

δ_{13C} (125.7MHz; DMSO)* 171.41 (C, [terpyNMe.NH<u>C</u>OCH_2CH_2]$_2$); 156.75 (C, C(4')); 155.70 (C, C(2'), C(6') or C(2), C(2")); 155.47 (C, C(2'), C(6') or C(2), C(2")); 149.24 (CH, C(6), C(6")); 137.31 (CH, C(4), C(4")); 124.26 (CH, C(5), C(5")); 120.94 (CH, C(3), C(3")); 103.43 (CH, C(3'), C(5')); 33.17 (CH_2, [terpyNMe.NHCO<u>C</u>H_2CH_2]$_2$); 24.80 (CH_2, [terpyNMe.NHCOCH$_2$<u>C</u>H_2]$_2$) m/z(ESI)= 665 (<10%, $[MH]^+$), 333 (100%, $[M+2H]^{2+}$). *A signal due to the primary C atom [terpyN<u>C</u>H_3.NHCOCH$_2$$CH_2$]$_2$ was not observed, probably due to it being obscured by the DMSO solvent resonance.

Adipoyl-Linked-Bis[4-Picoline(4'-Hydrazino-2,2':6',2"-Terpyridine) Platinum(II)] Tetrafluoroborate (V)

The general procedure for platination was carried out using acetone as the initial solvent using adipoyl-linked bis(4'-hyrazinoterpyridine) (20mg, 0.03mmol), diiodo(1,5-cyclooctadiene)platinum(II) (84mg, 0.15mmol) and silver tetrafluoroborate (80mg, 0.32mmol). Vigorous stirring and long reaction times (60 minutes) were required owing to the poor solubility of the terpyridine in acetonitrile. Recrystallisation from MeCN and diethyl ether gave yellow crystals of the title product (33mg, 67%): m.p.>200°C; (Found: C, 36.6; H, 3.4; N, 11.1; $Pt_2C_{48}H_{46}N_{12}O_2B_4F_{16}$ requires C, 36.9; H, 3.0 N, 10.8 $Pt_2C_{48}H_{46}N_{12}O_2B_4F_{16}$ .H_2O requires C, 36.5; H, 3.1; N, 10.7); ν_{max}(KBr)/cm^{-1} 3330-3200(s,br), 3087(m,br), 2360(w), 1690(m), 1625(s), 1483(m), 1100-1000(s,br), 788(m); δ_{1H} (500MHz; CD_3CN)* 8.77 (s, br, [Pt^{2+}pic.terpyN<u>H</u>.NHCOCH$_2$$CH_2$]$_2$ or [Pt^{2+}pic. terpyNH.N<u>H</u>COCH$_2$$CH_2$]$_2$); 8.74 (d, br, picoline H-C(2), H-C(6)); 8.34-8.17 (m, br, H-C(3), H-C(3"), H-C(4), H-C(4")); 7.60 (d, br, picoline H-C(3), H-C(5)); 7.55 (s, br, H-C(5), H-C(5")); 2.63 (s, picoline C<u>H</u>3); 2.54 (m,

1.0ml). The solid was then suspended in acetonitrile (0.5ml) and the mixture treated with a solution of 4,4'-vinylidenedipyridine (0.046g ; 0.25mmol) in dichloromethane (0.25ml). The mixture was kept at room temperature with occasional shaking for 5h. The solid changed to a paler yellow colour The product was collected by centrifugation and dried over P_2O_5 in vacuo to give the title compound (0.123g, 35%). mp. >230°C

Aquo 4'-chloro-2,2':6',2"-terpyridine platinum II tetrafluoroborate (I_{11})

Cyclooctadienylplatinum II diiodide (0.292g ; 0.53mmol) was treated with a solution of silver tetrafluoroborate (0.214g ; 1.1mmol) in acetone (1.5ml). The mixture was centrifuged to remove precipitated silver iodide and the supernatant solution added to a 2suspension of 4'-chloro-2,2:6',2"-terpyridine (0.133g ; 0.5mmol) in dichloromethane (0.5ml) and ether (0.25ml). The mixture turned yellow and a yellow solid was precipitated. This was collected by centrifugation and washed with ether (2 x 1.0ml). The solid was allowed to dry in the air and was then suspended in water (0.5ml). The mixture was sonicated in a water bath for 5min and then the supernatant liquor removed. Further water (1.0ml) was added and sonication continued for a further 5min. The resulting yellow solid was collected by centrifugation and dried over P_2O_5 *in vacuo* to give the title compound.

Ammonio 4'-chloro-2,2':6',2"-terpyridine platinum II tetrafluoroborate (I_{12})

Cyclooctadienylplatinum II diiodide (0.292g ; 0.53mmol) was treated with a solution of silver tetrafluoroborate (0214g ; 1.1mmol) in acetone (1.0ml). The mixture was centrifuged to remove precipitated silver iodide and the supernatant solution added to a suspension of 4'-chloro-2,2:6',2"-terpyridine (0.133g ; 0.5mmol) in dichloromethane (0.5ml). The mixture turned yellow and a yellow solid was precipitated. This was

centrifugation and washed with ether (2 x 1.0ml). The solid was allowed to dry in the air and was then suspended in water (0.5ml). The mixture was sonicated in a water bath for 5min and then the supernatant liquor removed. Further water (1.0ml) was added and sonication continued for a further 5min. The resulting yellow solid was collected by centrifugation and dried over P_2O_5 *in vacuo* to give the title compound.

Ammonio 4'-(4-bromophenyl)-2,2':6',2"-terpyridine platinum II tetrafluoroborate (Q_{12})

Cyclooctadienylplatinum II diiodide (0.292g ; 0.53mmol) was treated with a solution of silver tetrafluoroborate (0214g ; 1.1mmol) in acetone (1.0ml). The mixture was centrifuged to remove precipitated silver iodide and the supernatant solution added to a suspension of 4'-(4-bromophenyl)-2,2:6',2"-terpyridine (0.194g ; 0.5mmol) in dichloromethane (0.5ml). The mixture turned orange and a gum was precipitated. On rubbing this triturated to give a yellow solid which was collected by centrifugation and washed with acetone (1.0 ml), acetone : ether (1:1) (1.0ml), ether (1.0ml) and finally ether saturated with ammonia (2 x 1.0ml) to form the amine complex. This afforded the title compound as a yellow solid (0.265g, 68%).

4,4'-Vinylidenedipyridine bis[4'-(4-bromophenyl)-2,2':6',2"-terpyridine platinum II]tetrafluoroborate (Q_{14})

Cyclooctadienylplatinum II diiodide (0.292g ; 0.53mmol) was treated with a solution of silver tetrafluoroborate (0.214g ; 1.1mmol) in acetone (1.5ml). The mixture was centrifuged to remove precipitated silver iodide and the supernatant solution added to a suspension of 4'-(4-bromophenyl)-2,2:6',2"-terpyridine (0.194g ; 0.5mmol) in dichloromethane (0.5ml). The mixture turned orange and a gummy red solid was precipitated. Acetonitrile (025ml) was added and on rubbing the red gum

4-Picoline 4'-azido-2,2':6',2''-terpyridine platinum II tetrafluoroborat (Z)

Cyclooctadienylplatinum II diiodide (0.060g ; 0.11mmol) was treated with a solution of silver tetrafluoroborate (0.043g ; 0.2mmol) in acetone (0.5ml). The mixture was centrifuged to remove precipitated silver iodide and the supernatant solution added to a solution of 4'-azido-2,2:6',2''-terpyridine (0.027g ; 0.10mmol) in dichloromethane (0.5ml) and acetonitrile (0.25ml). The mixture turned yellow and a yellow solid was precipitated. This was collected by centrifugation and washed with acetone (1.0ml). The solid was suspended in acetonitrile and treated with 4-picoline (50ml ; 0.51mmol). The solid dissolved and the brown solution was kept at room temperature for 16h before being added dropwise to ether (7.5ml). The title compound was precipitated as a pale brown powder (0.061g ;82%) collected by centrifugation and washed with ether (2 x 1.0ml). mp >230°C (Found: C, 34.2; H, 2.4; N, 13.1. $C_{21}H_{17}B_2F_8N_7Pt$ requires C, 34.2; H, 2.3 N, 13.3%); ν_{max}(nujol)/cm^{-1} 2123 (N_3); δ_H(200MHz CD_3CN) 2.64 (3H, s, pyMe), 7.69-7.79 (6H, m, pyH3,5 and terpyH4',4'' and 5,5''). 8.00 (2H, s, terpyH3',5') 8.33-8.48 (4H, m, pyH2,6 and terpyH3'3''),8.72-8.86 (2H, m, terpy H6,6''); m/z(ESI) 281(M^{2+}).

Table 2

The 96 hour IC_{50} values (in μM) for the *in vitro* growth inhibition of human ovarian cell lines

Two of the cell lines are resistant to cisplatin and one to doxorubicin.

RF is the resistance factor: IC_{50} resistant line/IC_{50} parent line

Compound	CH1	CH1cis^R	RF	CH1dox^R	RF	A2780	A2780cis^R	RF	SKOV3
D	>100	>100	---	---	---	67	>100	-	>100
E	19.5	22	1.1	---	---	31.5	56		1.8
O	>100	>100	-	17.5	---	40	>100	-	>100
J	92	100	1	>100	---	41	50	1.2	>100
Y_2	56	61	1.1	40	0.7	80	90	1.1	47
I	6.35	6.4	1	0.425	0.07	14.5	14.5	1	5.6
M	5.4	5.5	1	1.5	0.3	44	50	1.1	50
N	15.5	16	1	5.1	0.3	25.5	94	3.7	45
P	7.2	8.9	1.2	1.5	0.2	27	25	0.9	13.5
Q	5.0	5.8	1.2	1.05	0.2	39	29.5	0.8	>100
T	4.6	3.7	0.8	4.2	0.9	7.7	20	2.6	19
R	16	13.5	0.8	5.3	0.3	39	89	2.3	80
S	65	>100	-	14.5	0.2	18	62	3.4	>100
X	15.1	16.5	1.1	17	1.1	25	21	0.8	25
V	48	42	0.9	40	0.8	19	40	2.1	98
W	48	46	0.9	58	1.2	17	10.5	0.6	>100

Table 6

% Inhibition at a Given Concentration

	Leishmania donovani					*Trypanosoma cruzi*					*Trypanosoma brucei*						
Compound	30μM	10μM	3μM	1μM	ED_{50}	30μM	10μM	3μM	1μM	ED_{50}	30μM	10μM	3μM	1μM	0.3μM	0.1μM	0.03μM
$I_{1.}$	T/100	T/100	99	99	-						100	100	100	100	0	0	
$Q_{1.}$	T/100	T/100	T/100	100	-						100	100	100	100	100	100	

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2. A complex as claimed in claim 1, where X is pyridine or 4-substituted pyridine.

3. A complex as claimed in claim 2, wherein the 4-substituent is methyl or halo.

4. A complex as claimed in claim 1, wherein X is ammonia or water or halide.

5. A complex as claimed in claim 1, which complex is a dimer in which each X is (-Py-CH=) where Py is pyridine.

6. A complex as claimed in any one of claims 1 to 5, wherein R' is 4'-(4-substituted)-phenyl.

7. A complex as claimed in claim 6, wherein the 4-substituent is methyl or bromo.

8. A complex as claimed in any one of claims 1 to 5, wherein R' is amine, e.g. NH_2 or NHR or NR_2, or hydrazine or alkylhydrazine or aziridine or azide.

9. A complex as claimed in anyone of claims 1 to 8, wherein the counterion is tetrafluoroborate.

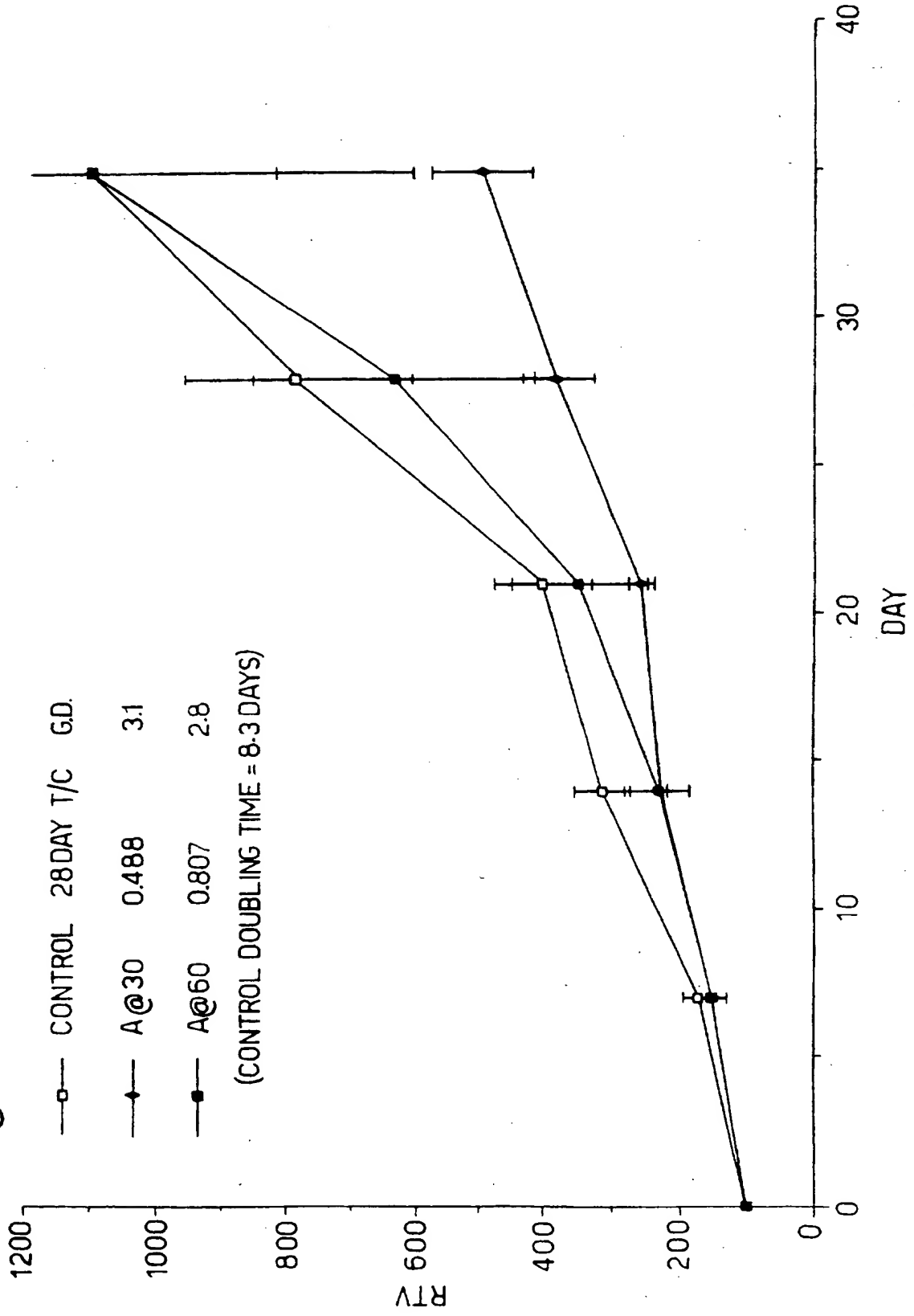
10. A complex selected from those designated A_1, A_3, A_{11}, A_{12}, A_{13}, A_{14}, I, P, Q, T, I_{12}, Q_{12}, I_{14}, Q_{14}, Z and Z_{14}.

11. A method of preparing an anti-tumour agent, which method comprises bringing a complex according to any one of claims 1 to 10 into a form suitable for administration.

12. A method of preparing an anti-protozoal agent, which method comprises bringing a complex according to any one of claims 1 to 10 into a form suitable for administration.

13. A method of making a 2,2':6',2"-terpyridine Pt(II) complex, which method comprises reacting a platinum complex of 1.5-cyclooctadiene (COD), or other strong bis-*trans*-labilising ligand, with a 2,2':6',2"-terpyridine in solution in the presence of acetonitrile.

Fig.1.


CONTROL 28DAY T/C G.D.
A@30 0.488 3.1
A@60 0.807 2.8
(CONTROL DOUBLING TIME = 8.3 DAYS)
RTV
DAY
0
200
400
600
800
1000
1200
0
10
20
30
40

INTERNATIONAL SEARCH REPORT

Int. Jonal Application No
PCT/GB 97/00218

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ACTA CRYSTALLOGRAPHICA, SECTION C: CRYSTAL STRUCTURE COMMUNICATIONS, vol. C52, no. 7, 15 July 1996, pages 1645-8, XP000197332 A. W. ROSZAK ET AL.: "2,2':6',2"-Terpyridine(1-methylimidazole-N3)platinum(II) Perchlorate Acetonitrile Solvate" see page 1645, formula (I) ---	1
X	JOURNAL OF THE CHEMICAL SOCIETY, DALTON TRANSACTIONS, no. 23, 1995, pages 3853-9, XP000670168 B. PITTERI ET AL.: "Nucleophilic Displacement of Halides from Monocationic Platinum(II) Complexes containing Neutral Tridentate Chelating Ligands with Sulfur and Nitrogen Donors: Kinetics and Equilibria" see page 3853, right-hand column, last paragraph to page 3854, left-hand column, first paragraph; page 3855, table 1, paragraph (d); page 3856, table 2, paragraph "L = terpy" ---	1
A	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 71, no. 10, 1974, pages 3839-43, XP000197321 K. W. JENNETTE ET AL.: "Metallointercalation Reagents. 2-Hydroxyethanethiolato(2,2',2"-terpyridine)-platinum(II) Monocation Binds Strongly to DNA By Intercalation" cited in the application see page 3839, figure 1 ---	1
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 28, no. 8, 1985, pages 1113-6, XP000670165 W. D. MCFADYEN ET AL.: "Activity of Platinum(II) Intercalating Agents against Murine Leukemia L1210" see page 1114, chart I ---	1
A	POLYHEDRON, vol. 14, no. 3, 1995, pages 451-3, XP000197341 G. ANNIBALE ET AL.: "New routes for the synthesis of chloro(diethylenetriamine)-platinum(II)chloride and chloro-(2,2':6',2"-terpyridine)platinum(II) chloride dihydrate" see page 452, left-hand column, lines 5-13 ---	1

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Form PCT ISA 210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/GB 97/00218

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 18 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.